MINI-REVIEW

Current status and future prospective of Curcumin as a potential therapeutic agent in the treatment of colorectal cancer†

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Abstract

Colorectal cancer (CRC) is the third most common cause of cancer-related deaths worldwide. Hence there is a need to identify new therapeutic agents that improve the current repertoire of chemotherapeutic drugs. The antitumor activity of curcumin has been reported for several tumors, including CRC. A recent phase I trial showed that curcumin is safe and tolerable adjunct to FOLFOX (5-fluorouracil, folinic acid and oxaliplatin) chemotherapy in patient-derived colorectal liver metastases at doses up to 2 grams daily. Another trial revealed the effect of combining curcumin with FOLFOX in patients with inoperable colorectal cancer. The aim of current review was to summarize the current knowledge about possible molecular mechanisms of curcumin in CRC with particular emphasis on preclinical and early clinical studies of colorectal cancer.

Key words: colorectal cancer, curumin, 5-FU, clinical trial

Introduction

Colorectal cancer (CRC) has the third highest prevalence of cancers, affecting men and women equally. It has a poor prognosis in its malignant stages; patient are rarely cured completely, and recurrence is common (1, 2). Patients do not respond to commonly used chemotherapeutic drugs and surgical procedures, due to surgical risk, toxicity and side effects of chemotherapy drugs(3). Thus, there is a need for low toxicity agents that be able to improve outcomes and decrease the side effects. Accordingly, using naturally substance, as phytochemicals including resveratrol and curcumin with chemo-preventive role in CRC, is a potential option (4, 5).

Curcumin, a nontoxic ingredient of turmeric originally isolated from the plant Curcuma longa, is a popular phytochemicals for prevention of tumor growth (6-8). Curcumin exerts anti-proliferative, anti-migratory and anti-invasive in CRC by interactions with number of molecular target including the transcription factor NF-κB, transforming nuclear factor-alpha (TNF-α), and AMP-activated protein kinase (AMPK) (7-11). It has been shown consistently that colorectal cancer stem cells (CCSCs) with tumor initiating and chemo-resistance properties are suppressed in response to curcumin. In this review, we aim to highlight the curative value of the curcumin and its analogues in clinical trials and summarize in vitro and in vivo studies.

Molecular mechanism of antitumor and anti-invasive effect of curcumin

Several studies have explored the underlying molecular mechanisms of curcumin to suppress tumor growth of CRC. Liu et al. evaluated the expression of peroxisome proliferator-activated receptor gamma (PPARγ) in rat colon mucosal tissues followed by evaluations of curcumin on CRC cell lines. The results indicated that curcumin suppresses 1,2-Dimethylhydrazine (DMH)-mediated colorectal carcinogenesis by suppressing the PPARγ pathway (12). In addition, the results of curcumin therapy in patients with advanced

CRC have indicated that forkhead box protein-3 (Foxp3) positive Treg frequency markedly reduced and the T helper 1 (Th1) frequency was significantly increased. Curcumin can convert Tregs to Th1 cells by suppressing Foxp3 expression and increasing interferon-gamma (IFN-γ) production. Thus, administration of curcumin regulates the function of immune effector cells that have a positive effect on treatment of advanced CRC (13). It has been shown that this natural compound also inhibits the growth of CRC by repressing the expression of cyclooxygenase-2 (COX-2) (14). Moreover, treatment of human colorectal carcinoma cells with curcumin induces caspase-3-mediated apoptosis by decreasing expression of p53 and pre-mRNA processing factor 4B (Prp4B) in a dose- and time-dependent manner (15). Anthwal et al. have reported that new analogues of curcumin (a series of C-5 curcumin analogues) suppress TNF-α-dependent activation of NF-κB in CRC (16).

Several studies have suggested that curcumin affects the cell-cell adhesion components and transcriptional factors for inhibition of tumor invasion and metastasis. For example, Chen et al. reported that curcumin inhibits invasion, cell migration, and colony formation in vitro and decreases liver metastasis and tumor growth in animal models. The authors observed curcumin downregulates Sp-1 transcription factor and its downstream signals and also suppresses focal adhesion kinase (FAK) that promote the expressions of several extracellular matrix components related to invasion and metastasis. Curcumin also regulates cell surface molecule CD24 and E-cadherin expression, which serves as an inhibitor of epithelial to mesenchymal transition (EMT) in CRC cells (17). A lipophilic analog of curcumin, Dimethoxy curcumin, inhibits the growth of CRC by downregulating survivin and upregulating E-cadherin of CRC cells (18). Dendrosomal curcumin prevents metastatic potential of CRC cells via downregulation of cell adhesion proteins including Hef-1, Zeb-1, and Claudin-1 (19). Similarly, Su et al indicated that curcumin suppresses invasion and metastasis of CRC via modulation of NF-κB and downregulation of COX-2 and matrix metalloproteinase-2 (MMP-2) expressions (20).

The AMP-activated protein kinase (AMPK) pathway, is a highly conserved sensor of cellular energy, has emerged as an important pathway implicated in cancer control. Interestingly, it has been shown that curcumin through AMPK-induced inhibition of NF-κB, urokinase-type plasminogen activator (uPA) activator and matrix metalloproteinase-9 (MMP9) inhibits CRC invasion (21).

Cell-cycle arrest and apoptosis

Increasing evidence indicates that curcumin prevent CRC proliferation with cell cycle arrest, and accelerates apoptosis. Curcumin and its analogs, EF31 and UBS109, downregulate Thymidylate synthase and its transcription factor E2F-1 by inhibited NF-κB, downregulated survival pathways and caused cell cycle inhibition (22). A novel analog of curcumin, EF24, effectively induces apoptosis through increasing intracellular levels of Reactive oxygen species (ROS) in CRC cells. EF24 also induces activation of caspases-9 and -3, related to downregulation of Bcl-2 expression and decreased Bcl-2/Bax ratio, activated intrinsic apoptotic signaling in CRC cells (23). Another derivative of curcumin, WZ35, induces ROS generation and endoplasmic reticulum (ER) stress in CRC cell line (24). Curcumin is capable to downregulate cell cycle protein cyclin dependent kinase 2 (CDK2) and subsequently lead to G1 cell cycle arrest (25). Similarly, Dasiram et al. studied the effect of curcumin on human colon adenocarcinoma cells with p53 mutation. They observed that treatment cells with curcumin inhibits the proliferation and cellular viability by cell cycle arrest at the G1 phase and diminish the cell population in the S phase (26).

ER stress and mitochondrial pathway

The induction of ER stress and mitochondria-dependent pathways can be via two mechanisms for the chemopreventive activity of curcumin in human colon cancer. For instance, in human colon cancer, curcumin- dependent proteasome inhibition leads to the accumulation of ubiquitinated proteins and several proteasome targets including p27 and p21/Bax, followed by inducing apoptosis (27). Further, a study has reported that curcumin

upregulates expression of caspase-3, cytochrome-c, Bax via inhibition of PI3K/Akt signaling pathway in CRC cells (28). Banerjee et al. observed that curcumin shifts oncogenic RAS-mediated apoptosis through MEK/ERK pro-proliferative signaling to p38MAPK/JNK1 pro-apoptotic pathway. This signal-switch leads to phosphorylation of p53, transactivate BAX and BCL2-binding component 3 (PUMA) genes, required for death of Human CRC (29). Similarly, curcumin disrupted the mitochondrial membrane potential and activated the mitochondrial caspase-3 and -9 in CRC. This compound also induces the release of cytochrome c with a significant increase of Bax and p53 and a marked reduction of Bcl-2 and survivin (30).

Glycolytic pathway

Curcumin inhibits CRC cell proliferation by alternate the glycolytic pathway and the enzyme involved. In parallel to this effect, it has been shown that curcumin promotes dissociation of glycolytic enzyme hexokinase II (HKII) from mitochondria via AKT-mediated phosphorylation and induces mitochondrial-mediated apoptosis in CRC. Furthermore, glycolysis, as a source of ATP production is perturbed by curcumin via down-regulation of HKII expression (31). Overall, the different molecular mechanisms modulated by curcumin summarized in Figure 1.

Combination therapy

Using curcumin in combination therapies can increase the anticancer effect of chemotherapy drugs for CRC. It has been reported that curcumin along with 5-fluorouracil's (5-FU) loaded in N, O-carboxymethyl chitosan nanoparticles, promotes the anti-cancer effects of these drug in CRC (32). Similarly, the combination of curcumin and oxaliplatin synergistically induce apoptosis through increased pro-apoptotic protein including Bax, caspase-3 and PARP, and reduced expression of anti-apoptotic proteins such as BCL-2, survivin and HSP70 in CRC (33). Chen et al showed that administration of curcumin along with perifosine, an oral bioactive alkyl-phospholipid, lead to the inhibition of Akt activity, the

suppression of cyclin-D1 and Bcl-2 expression. In addition, co-administration of perifosine and curcumin regulate activation of c-Jun N-terminal kinases (JNK) and downregulation of cyclin D1 and Bcl-2 account for growth inhibition (34). In addition, the anti-tumor effect of curcumin and 3acetyl-11-keto-β-boswellic acid (AKBA) studied in colorectal cancer. This suggests that curcumin and AKBA up-regulate miR-34a and down-regulate miR-27a in the presence of p53, leading the inhibition of cell proliferation and inducing metastasis in CRC (35). Moreover, curcumin overcame the resistance to radiation therapy through down-regulating NF-κB-mediated gene products including Bcl-2, COX-2, Inhibitor of apoptosis protein-2 (c-IAP2) and cyclin D1. Curcumin also via inhibition of IκB-α degradation, and Akt phosphorylation counter radioresistance. Hence, Curcumin blocks NF-κB signaling pathway and results in an enhanced antitumor effects of radiation therapy (36).

Colorectal cancer stem cells (CCSCs)

There is growing evidence suggesting effect of curcumin on CCSCs. A curcumin analogue, GO-Y030, inhibits the “signal transducers and activators of transcription 3” (STAT3) activity, which suppresses in vitro growth of CCSCs. The in vivo results confirmed that GO-Y030 is an inhibitor of STAT3 on mouse models (37). In support of the apoptotic potential of curcumin on CCSCs, Huang, et al. indicated that curcumin induces apoptosis of CRC cells as well as of CCSCs, only in CD44 cells. The authors suggest that curcumin might couple with CD44(+) witch blocked transport of glutamine into the cells, result in decline the glutamine content and leading apoptosis (38).

Curcumin in clinical phases

Bayet-Robert et al. have reported that the combination of curcumin and docetaxel was safe, practicable, and tolerable. In this study, the patients with metastatic mammary cancer received 0.5 g curcumin for seven consecutive days, while docetaxel (100 mg/m2) was injected as intravenous (IV) infusion every 3 weeks for six cycles. Moreover, the patients received 50 mg BID of methylprednisolone two days before and after chemotherapy. This

trial suggested that the recommended dose of curcumin in combination with docetaxel is 6000 mg/day (39).

Another trial investigated the effect of docetaxel with or without curcumin in patients with breast cancer (NCT00852332). Ryan et al. conducted a placebo-controlled, trial in breast cancer patients received 2 g curcumin three times a day orally followed by radiotherapy. A considerable decrease in radiation-induced desquamation and dermatitis observed (40). Another group examined the effect of nano-curcumin in patients with breast or gastrointestinal cancer. The patients received 12 tablets of nano-curcumin per day for 3 months (IRCT2014091418745N2).

the safety and effectiveness of MB-6 (extracted from some plants such as curcumin) in combination with chemotherapy in 60 metastatic colorectal cancer (mCRC) patients was evaluated by Chen et al. 29 patients received 6 × 320 mg oral capsules of MB-6 three times a day and 5-FU plus oxaliplatin (FOLFOX4) chemotherapy regimen every 2 weeks for 16 weeks. It observed that MB-6 can decrease the adverse effects and increased progression free survival (PFS) in patients with CRC (41).

A pilot study was conducted to measure the levels of curcumin in the colorectal tissue of patients undergoing colorectal endoscopy or resection. The patients received 5 × 470 mg oral capsules of curcumin C3 complex daily for 14 days (total 2.35 g curcuminoid). The tissue levels of curcumin were measured in bowel mucosa and found the pharmacological active level even after washing the tissue. These findings suggested that curcumin might be useful in CRC (42).

He and colleagues conducted a double blinded, randomized clinical trial to assess the effect of curcumin in 126 CRC patients who would undergo primary surgical therapy. 63 patients received 360 mg oral curcumin (in capsule form) three times a day before surgery. It found that curcumin can induce cancer cell apoptosis, depletion of TNF-α serum level and p53 expression (43).

Carrol et al. designed a non-randomized phase IIa clinical trial to determine the impact of curcumin on prevention of CRC in 41 smokers with eight or more Aberrant crypt foci (ACF) on colorectal screening. In the first stage, 22 participants were administered with 2 g curcumin (8 capsules) by mouth daily for 30 days. After evaluating toxicity, the study went to the second stage, which in 12 participants received 4 g curcumin (16 capsules) daily for 30 days. The results indicate that curcumin at the dose of 2 g and 4 g was tolerable and also might reduce ACF numbers (44). Garcea et al recruited 12 CRC patients into three different groups, that received 1, 4, or 8 oral curcuminoid capsules (450 mg curcumin + 40 mg desmethoxycurcumin + 10 mg Bisdemethoxycurcumin) for a week ahead of surgery. The results showed that 3.6 g curcumin is safe and other tissues of GI tract achieved very slight concentration levels of curcumin (45).

In patients with advanced CRC refractory, Sharma et al. conducted phase 1 trial with a different formulation to standard chemotherapies. 15 patients in five groups received 2, 4, 6, 8, or 10 capsules (220 mg each) for four months (each capsule was contained 18mg curcumin, 2 mg desmethoxycurcumin and 200 mg essential oil derived from Curcuma spp, the dietary polyphenol curcumin). These data suggest that Curcumin is safe (46). Sharma and colleagues evaluated curcuminoid capsules in 15 patients in four groups received 1, 2, 4, or 8 C3 500 mg daily up to 4 months (each capsule contained 450 mg curcumin, 40 mg desmethoxycurcumin, 10 mg Bisdemethoxycurcumin). Curcumin was well tolerated, except three patients who experienced nausea and diarrhea. In addition, the results showed 450-3600 mg curcumin up to 4 months is safe and 3.6 g/day curcumin was competent for evaluating the effects of curcumin on cancer prevention outside of the GI tract (47). A non-randomized trial conducted the safety, pharmacokinetics, and efficacy of irinotecan in combination with curcumin in mCRC patients (NCT01859858). Further open evaluated PFS in CRC patients with unrespectable metastatic who started Avastin/FOLFIRI in combination with curcumin (NCT02439385).

Inoperable metastatic CRC patients received oral curcumin with 12 cycles FOLFOX chemotherapy regimen. This study showed the safety, tolerability, and effectiveness of this approach (NCT01490996). A similar study assesses whether curcumin in combination with capecitabine and radiotherapy can constrict or slow the growth of rectal tumor. The safety of this combination and the impact of curcumin on complication of chemotherapy and radiotherapy in patients with adenocarcinoma of rectum have been studied (NCT00745134). The summary of clinical trial related to curcumin has been shown in Table 1 to investigate its anti-cancer potential.

Negative aspects of curcumin

Whilst there is increasing evidence suggesting the therapeutic potential of curcumin (48-55), but some studies indicated the adverse effects of curcumin. Curcumin has poor bioavailability due to inefficient GI absorption (56-58). Several methods have been developed to increase poor bioavailability (59-62). For instance, organogel-based nanoemulsion showed great improvement in curcumin bioaccessibility (63). In line with this, curcumin (500 mg/kg body weight) orally co-administered with piperine (a bioactive compounds in spices-turmeric, 20 mg/kg body weight) appears suitable to improve bioavailability and maintenance of curcumin in the body tissues (64).

In line with this, curcumin increases the degradation of p53, leading to the accumulation of DNA-damaged cells in healthy people(65). Ghoneim investigated the effects of curcumin on ethanol-induced hepatocyte necrosis in rats. The findings hinted that low concentration of curcumin induces an antioxidant effect by decreasing the release of cytochrome C and reducing lipid peroxidation (66). However, higher concentrations of curcumin reduced glutathione levels, activated caspase-3, and subsequently causes hepatotoxicity. Moreover, Jiao et al. reported that curcumin can reduce hemoglobin, hematocrit, serum iron, spleen and liver iron and also inhibits hepcidin synthesis(67). These findings showed curcumin

affects systemic iron metabolism, leading iron deficiency and anemia. However, several clinical evidence showed the safety of curcumin (68, 69).

Conclusion

There is limited data showing the anti-cancer potency of curcumin in CRC. It has been shown that curcumin is safe and can be used in combination with other chemotherapeutic drugs; its efficacies are limited by its low absorption. Moreover, further preclinical studies are warranted to explore the molecular mechanism of its action. Also most of the patients are become resistant to therapy, supporting further investigation on the value of this agent in this condition. Furthermore, detection of predictive biomarker is required to predict the response rate or identify patients who might benefit from therapy.

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Table 1. Summary of clinical trials with curcumin in CRC.

Enrollment	condition	Intervention	Allocation	Trial phase	Current status	Number of clinical trial/Reference
60	CRC	6 capsules (320 mg each) of MB-6 thrice a day + FOLFOX 4 chemotherapy regimen for 16 weeks	Randomized	Unknown	Completed	(41)
28	Undergoing colorectal endoscopy or resection or having CRC	5 capsules of daily oral Curcumin C3 complex for 14 days	Unknown	1	Completed	NCT00973869/ (42)
126	CRC	**Group 1:** 360 mg curcumin three times a day by mouth during the period ahead of surgery **Group 2:** vehicle three times a day by mouth during the period ahead of surgery	Randomized	Unknown	Completed	(43)
41	Smokers with 8 or more Aberrant crypt foci (ACF)	**Stage 1:** 2 g/day orally for 30 days **Stage 2:** 4 g/day orally for 30 days	Non-Randomized	2a	Completed	(44)
12	CRC	1, 4, or 8 capsules/day of Curcumin C3 complex for seven days before surgery	Unknown	Unknown	Completed	(45)
15	Advanced CRC refractory	1, 2, 4, or 8 capsules (450 mg curcumin each) per day for up to 4 months	Unknown	1	Completed	(47)
15	Advanced CRC refractory	2, 4, 6, 8, or 10 capsules (18 mg curcumin each) daily for up to 4 months	Unknown	1	Completed	(46)
23	Metastatic CRC	**Arm 1:** Oral Curcumin (1, 2, 3,or 4 g per day) for 4 days prior to irinotecan + 200 mg/m2 irinotecan IV, days 1 and 15 **Arm 2:** MTD oral Curcumin as determined in part 1 + 200 mg/m2 irinotecan IV, days 1 and 15	Non-Randomized	1	Ongoing	NCT01859858
44	CRC	**Avastin:** 5mg/kg iv on day1, every 14 days. Irinotecan: 180 mg/m^2 iv on day1, every 14 days. **Leucovorin:** 200 mg/m^2 iv on day1,2 every 14 days. **5-fluorouracil bolus:** 400 mg/m^2 iv on day1,2 every 14 days. **5-fluorouracil infusion:** 1200 mg/ m^2 iv on day1,2 every 14 days. **Curcumin:** 100 mg orally in nanostructural form	Randomized	2	Ongoing	NCT02439385
51	Metastatic CRC	**Arm 1:** 12 cycles of FOLFOX chemotherapy regimen alone **Arm 2:** 12 cycles of FOLFOX chemotherapy regimen + oral complex C3 curcumin daily	Randomized	1/2	Ongoing	NCT01490996

45	Adenocarcinoma of rectum	**Arm 1:** curcumin (4 g tablets by mouth twice a day) + radiotherapy (45 Gy once a day, for 5 days in a row for 5-6 weeks) + capecitabine (Xeloda) (825 mg/m^2 by mouth twice a day only on days of radiation) **Arm 2:** placebo tablet by mouth twice a day + radiotherapy (45 Gy once a day, for 5 days in a row for 5-6 weeks) + capecitabine (825 mg/m2 by mouth twice a day only on days of radiation)	Randomized	2	Ongoing	NCT00745134
100	Adenocarcinoma of the colon	Gemcitabine + curcumin + celecoxib in patients with colon cancer for 2.7-4.0 months	Randomized	3	Unknown	NCT00295035
35	Colon cancer	**Arm 1:** Curcumin tablets-3.6 g taken daily for 7 days **Arm 2:** Curcumin conjugated with plant exosomes tablets-taken daily for 7 days Arm 3: No intervention	Randomized	1	Unknown	NCT01294072
686	Breast cancer	2.0g curcumin three times/day orally over the course of radiotherapy plus one week	Randomized	2/3	Completed	NCT01246973
14	Breast cancer	450 mg curcumin daily by mouth for seven sequential day	Randomized	1	Completed	(39)
35	Breast cancer	2.0g curcumin three times/day by mouth for 4-7 weeks	Non-randomized	2	Completed	(40)
40	Breast cancer	12 tablets of nanocurcumin per a day (3 tablet, QID) for three months except during chemotherapy	Randomized	2	Ongoing	IRCT2014091418745N2
100	Breast cancer	**Arm 1:** curcumin alone **Arm 2:** curcumin with Taxotere	Randomized	2	Ongoing	NCT00852332
22	Breast cancer	0.5g curcumin twice a day for six weeks	Randomized	2	Ongoing	NCT01740323
180	Breast cancer	**Arm 1:** Curcumin-based gel applied topically TID on the first day of radiotherapy and continuing until 1 week after completion of radiation therapy. **Arm 2:** HPR Plus™ applied topically TID on the first day of radiotherapy and continuing until 1 week after completion of radiation therapy. **Arm 3:** placebo gel applied topically TID on the first day of radiotherapy and continuing until 1 week after completion of radiation therapy.	Randomized	2	Ongoing	NCT02556632

Figure 1. Molecular targets regulated by curcumin.

Abbreviations

CRC: Colorectal cancer, PPARγ: peroxisome proliferator-activated receptor gamma, Foxp3: fork head box protein-3, COX-2: cyclooxygenase-2, Prp48: pre-mRNA processing factor 4B, TNF-α: Tumor Necrosis Factor alpha, NF-κB: Nuclear factor-κB, CDK2: Cyclin dependent kinase 2, ROS: Reactive oxygen species, FAK: Focal adhesion kinase, Sp-1: specificity protein 1, MMP-2: Matrix metalloproteinase-2, AMPK: AMP-activated protein kinase, PI3K/Akt: phosphoinositide-3-kinase/ Protein kinase B, HKII: hexokinase II.